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(1) Jeans, P. C., in A. M. A. Handbook of Nutrition, ed. 2, Philadelphia, Blakiston, 1951, pp. 275-278.

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THE IRRADIATION EFFECTS OF THERAPY OF THE THYMUS GLAND IN RELATION TO THE PRODUCTION OF THYROID CARCINOMA*

Chairman: Isidore Lattman, M.D., Radiologist, Children's Hospital
Discussed by: Theodore Winship, M.D., Pathologist, Garfield Hospital
Calvin T. Klopp, M.D., Director, George Washington University Cancer Clinic
Ralph M. Caulk, M.D., Senior Attending Radiologist, Garfield Hospital
S. F. Williams, Captain MC USN, Chief of Radiology, U. S. Naval Hospital
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Harry L. Berman, Colonel MC USA, Chief, Radiation Therapy Section, Walter Reed Army Hospital
Edgar P. Copeland, M.D., Chief of Staff, Emeritus, Consulting Staff, Children's Hospital

Dr. Lattman:

One of the reasons that I arranged this meeting is because I have had a number of telephone calls from the parents of children who have received irradiation to the thymus gland. These parents read an article in the newspapers by Dr. Dwight E. Clark of Chicago, reporting his surgical treatment of 13 cases of carcinoma of the thyroid and two others which he followed but did not operate upon, all of whom had previously received irradiation to the thymus gland. (This article was published recently in the J.A.M.A.) While he does not state so directly, he does imply that 100 per cent of those who received irradiation developed cancer of the thyroid.

So far as I know, there have only been four cases of cancer of the thyroid in the period from 1914 and 1955 at this hospital. One of these cases was a girl, age 10, who was referred by Dr. McLendon. We thought it was either miliary tuberculosis or sarcoidosis. A small discrete nodule was removed from the right supraclavicular region. The pathological diagnosis was inconclusive, varying from granuloma to possible or probable sarcoidosis. The child died here and at autopsy carcinoma of the thyroid with metastasis to the lungs was found and confirmed histopathologically. This patient never received radiation therapy.

We have had quite a time in the x-ray department with this problem. I want to state that we do not irradiate thymus glands promiscuously. The

* From a discussion at a meeting of the Tumor Board on September 14, 1955.

pediatricians send the patients in for treatment. The classical symptoms are choking, stridor, cyanosis and spitting up. We then take films in the anterior-posterior and lateral views and unless we are sure that the thymus is enlarged by our measurements and we find the trachea to be displaced dorsally and compressed we do not treat the patient. It has been our routine here to give the patient 75r's anteriorly and 75r's posteriorly, (3 mm. of aluminum filter; 25 cm. distance; 120 K.V. and 5 M.A.; portal 10 x 10 cm.). The patient returns in two weeks after treatment, usually free of the symptoms, for a comparative x-ray study. In most cases we find the thymic shadow to be within normal limits and clinical symptoms either gone or markedly improved.

One of the cases I have in mind is as follows: one of our pediatricians called me late at night to Columbia Hospital. The child was cyanotic and had marked stridor. We x-rayed the child. There was an enlarged thymic shadow and in the lateral view the trachea was compressed and displaced dorsally. We did not have a therapy machine at Columbia Hospital and I asked that the child be transferred to Children's Hospital for therapy. In this case we took three films. The first one was too dark so we took another. It may well be that the exposure to the x-ray was sufficient, because the child improved markedly the next morning and no further therapy was indicated.

Recently there was an article published in *Radiology* (June 1955) by Dr. Simpson and her associates in which they studied 1,400 cases who received x-ray therapy to the thymic region. Contrary to Dr. Clark's report they did not find 100 per cent developing cancer but rather .004 per cent. Whether that is much higher than the expected occurrence remains to be seen. We do not know. As you are well aware, statistics are of great value in medicine, but unless they are handled by competent and experienced medical statisticians they can be terribly misleading. It behooves the physician who is going to publish an article in which statistics are to be used first to take the data to a medical statistician and see whether the data is worth publishing. Incidently, may I add that the work reported in *Radiology* was gone over carefully by competent medical statisticians.

Dr. Winship, who has been interested in thyroid disease for a long time has published a series of articles on the thyroid and I know of two of them that I have read carefully. One of them was in *Surgery, Obstetrics and Gynecology* of August 1955 and one of them was in the Bulletin of the *American Cancer Society*, May 1955, Vol. 5, No. 3, in which he reported 262 cases with a 10 per cent incidence of cancer of the thyroid in those who had previously received irradiation over the thymus. In his *Surgery, Obstetrics and Gynecology* article he has gone up to 14 per cent. Now he tells me that since then, in further studies, the percentage has gone up to 16 per cent.

In Dr. Simpson's article, she cogently points out that "a serious limitation to the interpretation of these data is the absence of a proper control group of untreated cases of infants with enlarged thymuses". Simpson compared her cases with enlarged thymuses that were treated to 1,400 siblings, none of whom had enlarged thymuses. Since the physiology of the thymus is obscure, one can not tell what influence an enlarged thymus may have on producing carcinoma of the thyroid or leukemia. Incidently, the percentage of leukemia in the 1,400 cases treated was slightly higher than cancer of the thyroid. There were 6 cases of cancer of the thyroid and 7 of leukemia in the 1,400 cases studied.

In the last five years we have had a large number of leukemia patients in our hospital. I have interrogated 30 of them and their parents and not one of them had received irradiation to the thymus. Many of them had never even been x-rayed before.

This concerns us here because there are instances where we are forced to treat thymuses. Dr. John Caffey of New York came here and delivered a talk opposing the treatment of thymuses but admitted that even he treats some cases and stated, "these are the cases that I have been forced to treat".

I called this meeting to discuss this problem and to get the pros and cons on this subject. I want to call on Dr. Winship next to let him say a few words. I concur with you, Dr. Winship, that we should not treat enlarged thymus cases promiscuously.

Dr. Winship:

A few weeks ago when the subject of irradiation to the thymus gland was mentioned at the Tumor Board, I had no idea the discussion would develop into such a meeting as this.

Five years ago, Duffy and Fitzgerald[1] reported 28 cases of carcinoma of the thyroid in young people below the age of 18. Ten of the group had received irradiation to the thymus gland during infancy and with that information other people began to look around. Simpson[2] published her series of 1,400 patients who had received irradiation to the neck during infancy. Six of these eventually developed thyroid carcinoma. Following this came Clark's[3] paper. He reported 13 cases of thyroid carcinoma, all of whom had received irradiation to the neck for either an "enlarged thymus gland" or some lesion on the neck. I had started a survey of childhood thyroid carcinoma in 1948 but only during the past five years have I inquired about a history of irradiation. Many of my cases come from pathologists and the histories are not complete but I have found 27 cases[4]. Counting all the known cases in the United States, of childhood with carcinoma of the thyroid, almost 20 per cent have had irradiation to the

thymus gland or to the neck for some other disease. This is a significant percentage. These figures should be recalled when we plan to irradiate a child who has difficulty in breathing.

Some additional information was suggested during the Tumor Board by Connally a few weeks ago, who quoted an article by Court Brown and Abbott[5]. They found that 25 of 2,361 patients with ankylosing spondylitis, treated with x-rays, developed leukemia. The expected rate of leukemia for a group of this size was 3.9 patients. I mention this only because the results are similar to those in children irradiated for thymus enlargement who develop thyroid carcinoma.

Another thing which strikes me as interesting is that every one of the cases of thyroid carcinoma following irradiation occurred in the United States. In canvassing Western Europe for cases of childhood thyroid carcinoma, I failed to find a single case treated by irradiation. They say they do not treat patients with enlarged thymus glands by irradiation.

I know of one surgeon in the middle west who does hare lip and cleft palate work, and because a patient died 20 years ago of some unknown cause he still is irradiating the thymus gland in every patient preoperatively.

I do not believe the statistics quoted by Dr. Lattman. I refer to his statement that none of the patients who had irradiation in this hospital have ever developed carcinoma of the thyroid gland. This must be regarded as an impression for I doubt that all these patients were followed for 20 years. There is a difference between statistics and impressions.

I should like to add a quotation from Potter.[6] "To my knowledge hyperplasia of the thymus has never been proved to have been a cause of death in the neonatal period".

I have two additional points which I think might be of interest. One point is: some of these cases of childhood thyroid carcinoma, as Dr. Lewis pointed out three weeks ago, very possibly had carcinoma at the time they were irradiated, because in our group of 321 children with thyroid cancer, twelve had a tumor, presumably carcinoma, at birth. The second point is that in the city of Washington during the past ten years there have been 10 cases of thyroid carcinoma in children and 3 of them had irradiation of the thymus gland.

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Dr. Klopp:

I became interested in this subject several years ago and felt that if there was an association between an enlarged thymus and thyroid cancer, it might be either because of some embryological development resulting in both the enlarged thymus and the production of a defect, which later manifested itself as thyroid cancer, or else perhaps irradiation played a role. To determine which was correct, we went back and looked up everything that we could find on the thymus in youngsters, its relation to the thyroid, and whether there was any relationship between the two. I am sorry to say that what is written on the thymus in most instances is not worth reading, but at least what we could find would suggest that no one had ever found that an enlarged thymus was in any way associated with any specific thyroid abnormality. As a further check, we made it our practice to dissect out the superior mediastinum whenever possible in children or adults who had thyroid cancer. We found in a certain number of young adults that there was thymus tissue present and rather sizable amounts of it, but again it became very difficult to decide whether or not this was an abnormal amount of thymus, because we did not have much to compare it with; and here we can criticize the pathologists. Most pathologists who do autopsies do not pay much attention to the thymus. As a matter of fact they sometimes do not even identify it. Again, we did not have very much with which to compare our findings. We have not followed this study much further because we did not think it worth the effort, but at least so far as we went we could not find any relationship between an enlarged thymus and any specific thyroid abnormality.

As far as the question of irradiation is concerned, in the patients with thyroid cancer that I have seen and/or treated, the percentage with a history of previous irradiation to the neck would be higher than that found by Dr. Winship; and I think that it would be still higher if we had correct information; for as soon as I got interested in this possible correlation I began to talk a little more closely with the patients involved and I might give you an example of just what I sometimes found.

We treated a young man of 23 with carcinoma of the thyroid. We talked with him and his father, and obtained no history of irradiation. It so happened that his father and mother were separated, and the night before his second operation the boy had a telephone call from his mother who lived

in Illinois, and had not communicated with his father for years. She wanted me to know that as a child he had had an "enlarged thymus" and had had irradiation to it. She thought that perhaps I ought to know, because possibly it had something to do with what he had now. Had she not called we would have had no information of his having had previous irradiation.

Certainly not all patients with thyroid cancer have received irradiation of the thymus and not all who have had irradiation have had an enlarged thymus. We have one who had received it for tuberculosis of cervical lymph nodes. The irradiation was given when the child was about 4. This is one of Dr. Winship's cases in which carcinoma of the thyroid showed up at the age of 15. We have a young man of 35 with cancer of the thyroid who received irradiation for acne at the age of 17. We have another man, whose findings were quite unusual although now I am no longer sure how to classify his pathology. This man had a very heavy beard at the age of 25 and accepted local irradiation treatment to get rid of it. At the age of 50, he now shows up with both a carcinoma of the pharynx and what was thought to be carcinoma of the thyroid, but may turn out to be a recticulum cell sarcoma. I think there is some relationship here between the two malignant tumors and the previous irradiation.

Irradiation is potentially very dangerous. I think we should use it very, very carefully. Any time we want to use it to treat a benign lesion we ought to go home and sleep on our decision before we begin. Obviously, it must be used in the treatment of certain malignant tumors, but even here we must remember that irradiation is potentially a very dangerous form of therapy.

Dr. Caulk:

I can see why Dr. Lattman is disturbed. I was not aware that this newspaper article had been published about Dr. Clark's work. I personally have no reason to discuss the syndrome of so-called "thymic disease". We have very little occasion to treat the thymus at the Garfield Memorial Hospital.

It seems to me that there is a considerable degree of fallaciousness in the articles of Drs. Simpson, Winship and Clark, and while they do not state specifically that x-ray therapy has caused the thyroid cancers, the implications are quite strong.

The fact must be accepted that ionizing irradiation can produce cancer under certain conditions. There is certainly evidence that it has in some cases produced cancer of the skin, and we must remember that in the large number of patients treated at Walter Reed Hospital during the war, who were subjected to heavy post-operative irradiation for testicular tumors, there were one or two cases that developed sarcoma of the bone.

I had the privilege of reading the pre-publication manuscript of Dr. Clark's article, which states: "All the cases of carcinoma of the thyroid in children and adolescents known personally by the author had been sub-

jected to prior irradiation to areas where the thyroid gland or portions of it *could* have been included in the field of irradiation".

Now actually, in Dr. Clark's group, there were only five cases that were treated for supposed thymic disease. The other cases were treated for cervical adenitis, enlarged tonsils and adenoids. Those of us who treat patients with roentgen therapy know that we have means of sharply limiting the beam and directing it to the area requiring the treatment. This is done by means of lead masks, lead lined cones, etc. If Dr. Clark's assumption is true, one would have to think that there would be an indirect effect, because after all, the tonsils, the adenoids and even much of the cervical adenitis is anatomically quite far removed from the thyroid gland. At least in my own experience (and I think we must assume this to be true of other therapists) the thyroid gland was *not* in the field of radiation and consequently there would be no direct effect. The same arguments would apply in the cases in which the thymic gland was irradiated. I regard the thymic gland as being below the clavicle in the upper mediastinum. Certainly again, the field of radiation in these treated cases is limited to that zone and as a consequence the thyroid gland would not be expected, either theoretically or practically, to receive direct radiation.

It would seem to me a more proper approach to consider that these infants who were treated for thymic disease had something wrong with them and we have not as yet entirely disproved that the thymus may be partially responsible. It may be that rather than the irradiation causing the cancer, there is some relationship between the thymic gland and thyroid cancer, which has not as yet been appreciated. It seems to me that the latter hypothesis is just as much, if not more tenable, than the assumption that these cases of thyroid cancer are produced by irradiation, as indicated in the arguments that have been presented.

Captain Williams:

I came to this meeting hoping to glean a few pearls. This discussion is not a new one to me but a frequent one during my duty at the University of Chicago and in the Memorial Hospital area at the Navy Hospital, St. Albans, N. Y. I think it is very easy to become disturbed over this subject and one should be familiar with it. My remarks reflect my own personal feelings for which I have no scientific proof. In the Navy, I have in the past treated many enlarged thymuses. Unfortunately I have a very poor follow-up on these cases for the reason that both the patient and myself are transferred and separated in a matter of months to a few years and follow-up is impossible. To my knowledge, none of the cancer cases I have treated have previously been treated for enlarged thymus. This does not mean that such a thing could not occur, rather it has just not occurred in my experience.

One should carefully examine the backgrounds of the institutions that

report these facts. One would find that there is a tremendous concentration of cancer cases at these hospitals. The isolated cancer case that is discovered in a midwestern state and arrives at one of these treatment centers is multiplied by the 48 states. A consideration of an unusual correlation of events, such as this I am sure, is therefore possible. The percentages and the number of cases that such a fact represents could therefore be quite erroneous or not representative of the true facts. There may be some background for such ideas but I believe that you have answered the problem already in what I have heard here today. In essence, one should not treat benign conditions unless there is a real reason for doing so and the risk entailed is warranted. If one thought that a baby was in danger of strangling of course one would treat him even though the risk of a future cancer was high.

I do not treat lymphoid hyperplasia of the nasopharynx if I can avoid it, unless there is beginning deafness or other complication of importance to the child. In these cases the risk is warranted. I think one should look at all therapy cases in this manner.

Dr. Andrews:

I have enjoyed the opportunity of hearing this discussion. Like others who have spoken I, also, have strong opinions about this. Two things occur to me. One is that I think that under certain circumstances ionizing radiation does induce changes which ultimately result in cancer. The second is that any unnecessary ionizing radiation is undesirable radiation. I no longer treat the thymus with ionizing radiation as I have come to have the strong feeling that there is no necessity or indication for such treatment. In other words, I do not hold to the idea that the thymus produces such symptoms as to require a reduction in the size of this organ. On this basis there is, therefore, no necessity for treating it and on the basis of the other considerations such treatment is undesirable.

Col. Berman:

I think that the case for the radiologist has been rather ably upheld by Drs. Lattman and Caulk. My experience with the so-called enlarged thymus has been limited. I have been very conservative in treating them. For one thing, I am not convinced about the accuracy of such a diagnosis. Frequently, I have been unable to distinguish it from an atelectatic upper lobe of the right lung. The question of displacement of the trachea sometimes comes up in the diagnosis, but the trachea in infants is a loosely fixed tube which moves around in the throat and these changes in position cannot be considered as evidence of displacement.

I am not yet convinced that irradiation produces the thyroid malignancies

and the leukemias that have been described, especially in this one article. However, the fact that a hazard has been pointed out is sufficient evidence for me to proceed conservatively. In the few thymuses that I have treated I have tended to stay on the low dosage side. If irradiation sufficient to produce a small collection of films (I do not know how much that would be) is enough to relieve symptoms, then I an inclined to think that small treatment doses are adequate. I have given a single dose of 25r with the 200KV machine, perhaps repeated once and only once. This is a skin dose, which means it includes the air dose and the back-scatter. I notice in this one article that 200r is claimed to be the critical dosage level. I do not know where that 200r is, whether it represents tumor, air, or skin dose. Furthermore, I notice in this article that some of the treatment fields were of the order of 15 x 15 cms. in size, which covers an awful lot of baby. Such fields are too large.

There is one other point which we should bear in mind and that is the irradiation of the fetus. Recently in searching for a film showing an early fetal skeleton in utero, I found a series of films of lumbar spine and pelvis showing this feature in a girl who had visited an orthopedic surgeon for backache. During the x-ray examination 11 films showing the pelvis were made. While it is true that the orthopedic surgeon did not know that this girl was pregnant, the exposure from 11 films on an early fetus is undoubtedly too much and might be a factor in upsetting the balance between carcinogenesis and lack of it, whatever that might be.

My own position with regard to the development of malignancies after thymus irradiation is that while I am not yet convinced a causal relationship exists, I am not going to dismiss this subject lightly. I am one of those persons who think that cigarettes have something to do with lung cancer. I am sure there are individuals in this room who adhere to a contrary view, but I will still hold to my belief until someone proves otherwise. Similarly with irradiation of the thymus; if a hazard is involved, we should not ignore it.

Dr. Copeland:

I hardly feel that I can contribute anything of real value to this discussion. I have, however, learned a great deal this morning. I am reminded of something that Cicero said many years ago, "Man believes true, those things which he wishes to be true". Apparently statistics can be used to prove or disprove the opinions in this controversy. I have never had the experience of having a patient with thyroid malignancy, and that covers a good many years and a good many patients. In the past ten years I have seen patients with symptoms attributed to enlarged thymus much less frequently than before. X-ray therapy was never used at my suggestion

until other possible causes had been excluded, and only after films suggested thymus enlargement. The interpretation of the films can be controversial. I have no knowledge of the dosage employed, but the patients invariably responded and there was usually a shrinking of the shadow. I should like to echo the opinions of some of the gentlemen expressed here this morning with respect to x-ray therapy, viz., that as the years go by I have become increasingingly fearful of irradiation in any of its forms in therapy. I have no doubt of the great advances made in its employment, but am more and more convinced that it should be in the hands of radiologists of great experience using apparatus making possible its most exact control.

HEMOPHILIA WITH FATALITY FOLLOWING FEMORAL VENIPUNCTURE

Case Report and Discussion

Jack J. Rheingold, M.D.
James H. Stallings, Jr., M.D.

Bleeding defects in children necessitate consideration of the new concepts of blood clotting mechanism as well as the dangers of pathological bleeding as a result of trauma or medical procedures. The unfortunate outcome of the present case of hemophilia has prompted the active Medical Staff of Children's Hospital to "prohibit the drawing of blood or the giving of any intravenous medication using the deep blood vessels of the thigh in any patients known to be or suspected of being a bleeder".

CASE REPORT*

D. S., a 1 year old white boy was in apparent good health until two months before admission when it was noted that large hematomas developed in the buttocks following injections of penicillin for respiratory infection. He had always bruised easily. On the day before admission blood was obtained for bleeding work-up by right femoral venipuncture. Although there was difficulty in obtaining blood, there was no immediate bleeding following this procedure but the next morning a hematoma at this site was noted by his mother. His private physician examined him and advised hospitalization. Family history indicated that a maternal uncle died from bleeding following circumcision.

On admission the boy had a temperature of 100.8°; his pulse rate was 120. There was slight icterus of the skin. In the right inguinal area was a large purple hematoma extending down the upper thigh. The thigh measured 36.2 cm in diameter. Bleeding work-up on the day before admission included: Bleeding time, 1 minute; Lee-White

* From the private service of George J. Cardany, M.D.

clotting time, 5 minutes; Siliconized Lee-White, #1, 5 hours, 15 minutes, #2, 5 hours, 45 minutes, #3, 5 hours, 55 minutes. Examination of peripheral blood on admission included: Hemoglobin 6.0 gm per 100 ml., Hematocrit 21 per cent, WBC 19,500 with Segmented Forms 40 per cent, Bands 13 per cent, Lymphocytes 43 per cent, Monocytes 4 per cent.

Treatment consisted of sedation and close observation of the hematoma which did not increase in size. At 9 A.M., on the day following admission he was found in profound shock. Phlebotomy was performed and plasma infusion begun under pressure. Death occurred after only 40 cc was given.

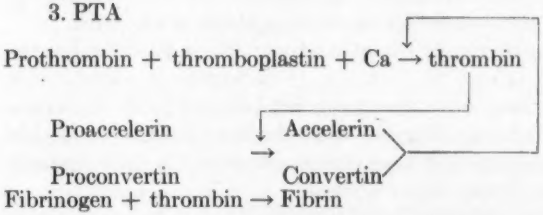
DISCUSSION

Jack J. Rheingold, M.D.

In March 1954, the journal *Blood* published a symposium entitled, "What is Hemophilia?", with more than half a dozen articles bringing up to date the opinions which characterize the thinking about this fascinating and sometimes bewildering disorder. Unfortunately there was not complete agreement but as Dameshek has said, "Out of confusion, however, often comes new clarity".

In general, however, most hematologists agree that hemophilia is a deficiency disease—not a deficiency of a single substance, as once believed, but one of at least three factors. To understand this, a review of the currently-accepted theory of coagulation is in order:

Plasma Factors + Platelet Factor → thromboplastin
1. AHG
2. PTC
3. PTA



As can be seen from this diagram, an enzyme derived from the rupture of platelets combines with the plasma factors to form thromboplastin. This substance, plus prothrombin, yields a small amount of thrombin, which then converts two accessory and accelerator factors to the active substances, accelerin (labile substance), and convertin (stable substance). These factors then speed up the conversion of prothrombin to thrombin. Fibrinogen is then changed to fibrin by the interaction with thrombin.

In hemophilia, there is a deficiency of one of the plasma factors. Previously, it was believed that a single substance, AHG or anti-hemophilic globulin was the only factor involved. In 1947, Pavlovsky observed that

the combined blood of two patients with hemophilia had a shorter clotting time than that of either patient. He assumed that anti-hemophilic globulin was probably not involved in the pathogenesis of hemophilia. However, in 1952, Aggeler and White studied a boy with a hemophiliac-like disease, who had a prolonged clotting time which could be corrected by the addition of typical anti-hemophilic plasma. They felt this was a variation of hemophilia, and called the new defect, PTC, or plasma thromboplastin component. Biggs and others in England described 7 patients with this same defect and called it "Christmas disease", after their first patient. In 1953, Rosenthal reported a family with a mild hemorrhagic disease in which the deficiency of a third factor, plasma thromboplastin antecedent, could be determined by various physical and chemical characteristics. Since that time many other patients with these variations have been found. Frequently, from a clinical standpoint one may be unable to differentiate the three, although in general PTA deficiency is a milder disease and may be found in the female sex. They can, however, be distinguished as follows:

Defect corrected by:	AHG	PTC	PTA
$BaSO_4$ treated plasma	+	−	+
Normal serum	−	+	+
Normal plasma	+	+	+
Fraction 1	+	−	−

There are other characteristics which distinguish these three substances, but from a practical standpoint, the response as above is adequate.

It is highly possible that other plasma factors may be discovered as this subject is pursued.

As suggested earlier, the above theories are not accepted by all. Tocantins, for example, has an entirely different idea. He believes that the plasma factor consists of a conjugate of a platelet co-factor and a lipid inhibitor. In normal clotting, a platelet factor is released by rupture of platelets and the conjugate (platelet co-factor/lipid inhibitor) dissociates, the platelet factor combined with the co-factor forming thromboplastin. In hemophilia A (or AHG deficiency) he postulates an excess of lipid inhibitor; the amount of platelet material cannot overcome this excess and the interaction of platelet lipid and its plasma co-factor is prevented or slowed. He has shown that the delayed clotting time in hemophilia can be shortened by dilution (down to 10 per cent blood concentrate) with physiologic salt. Hemophilia B (or PTC deficiency) he explains as representing a deficiency of the platelet co-factor.

In the laboratory, hemophilia is recognized by a normal bleeding time (since small vessel bleeding is largely controlled by vessel wall contraction)

and a prolonged clotting time in glass. Occasionally, the glass clotting time is normal. In performing this test, a clean venipuncture is necessary. To avoid the possibility of shortening the clotting time by means of tissue thromboplastin, once the venipuncture is done, the initial syringe is removed and blood drawn into a second clean syringe. When, however, a plastic tube is used or glass tube is coated with silicone, the clotting defect is magnified and a prolonged clotting time will be obtained. In addition, the plasma recalcification time is prolonged and the prothrombin consumption time is abnormal. When the diagnosis of hemophilia is made, differential studies using $BaSO_4$ treated plasma and serum will differentiate the types of hemophilia.

In regard to treatment, there are a number of agents which may reduce the clotting time to normal and improve the clinical status. These are fresh whole blood, fresh frozen plasma, plasma lyophilized when fresh and Fraction 1 of Cohn (which contains the anti-hemophilic globulin). It has also been demonstrated that stored plasma (ineffectual in AHG deficiency) will correct PTC deficiency. Not infrequently, however, correction of the in vitro clotting time may not be accompanied by a cessation of bleeding. This may be seen in hematuria or bleeding into internal organs following trauma.

In regard to joint involvement, conservatism is important. Rest and the use of cortisone are helpful during the acute attack. Gentle massage and other physical therapy are important during the convalescent phase. When joint deformities have occurred, orthopedic care by mechanical means (such as casting and wedging) should be used.

Surgery is absolutely to be avoided in the hemophiliac, unless the patient's life is otherwise in jeopardy. It should be remembered that symptoms of an "acute abdomen" may be caused by retroperitoneal or abdominal bleeding. The use of antibiotics and other tools of conservative management will frequently help in resolving the problem.

SUMMARY AND CONCLUSION

In conclusion, hemophilia is probably due to a deficiency of one of several plasma factors. Recent knowledge has indicated at least 3 hemophilioid states which may be differentiated in the laboratory. Treatment consists in the use of fresh whole blood, fresh frozen plasma and Fraction 1 intravenously. Conservative management of internal bleeding should be the rule.

CAT SCRATCH DISEASE

Report of Two Cases

James H. Stallings, Jr., M.D.

The positive diagnosis of cat scratch disease has been made in only four cases at the Children's Hospital. Two of these, a seven year old white boy seen in 1952 and a thirteen year old white boy seen in 1953, were studied outside the Hospital and admitted only for lymph node biopsy. They will not be reported here.

Case Reports

Case 1. K. H., a two and one-half year old white girl, was admitted to the private service of Dr. S. L. Blumenthal on September 14, 1954, with a history of fever as high as 103° for five days and a 1.5 cm. swelling in the right supraclavicular region of three days duration. Six weeks before admission she had been scratched on the right upper anterior chest by a playful kitten. Physical examination on admission was normal except for the scratch marks which were outlined by small, crusted vesicles, and the 1.5 cm. firm, non-tender supraclavicular lymph node. Pertinent laboratory data included a white blood count of 21,000 with 49 segmented forms, 3 bands, 46 lymphocytes, and 2 monocytes, Tuberculin (PPD) skin test, serological test for syphilis, multiple febrile agglutinations, and blood culture all were negative. Using both Green and Horn antigens, positive skin tests to cat scratch disease were recorded. She was treated with oral tetracycline and discharged on the fifth hospital day asymptomatic but with persistent enlargement of the solitary supraclavicular node.

Case 2. G. R., an 11 year old colored boy, was first seen November 13, 1954, in the Out-Patient Department with tender swellings about four cm in diameter in the right epitrochlear and axillary regions of six weeks duration. There was no history of contact with cats or rabbits and no evidence could be obtained of any trauma to the extremity. About three weeks after appearance of the lymph node enlargement, fever, anorexia, and malaise developed. The fever seemed to respond to penicillin administered by his family physician, but malaise and anorexia persisted. He had been found tuberculin positive in 1952 and chest x-ray at that time had been normal.

Tentative diagnosis of pyogenic adenitis was made and treatment with penicillin and sulfonamides instituted. White blood count was 16,600 with 41 segmented forms, 19 bands, 37 lymphocytes, and 3 monocytes. He showed positive skin tests to Tuberculin (PPD) and Green antigen. Chest x-ray (plate 1), showed numerous scattered areas of millet-sized calcification throughout both lung lower fields.

Because of the unknown nature of the pulmonary lesions, he was admitted to the Staff Service of Dr. W. F. Burdick on November 17, 1954. Physical examination was normal except for a four cm. fluctuant right epitrochlear node and a three cm. firm, non-tender right axillary node. Multiple agglutination tests were positive only for typhoid (H) 1:160 and typhoid (O) 1:320. Heterophile agglutination was negative. Histoplasmin skin test was positive. Gastric washings were negative on culture and guinea pig innoculation.

He remained afebrile and did not display constitutional symptoms during his hospital stay. He received oral tetracycline for ten days.

Twelve ml. of yellow-green pus was aspirated from the epitrochlear node on November 17th, and eight ml. on November 19th. This material was cultured for

X-ray shows numerous scattered areas of millet-sized calcification throughout both lower lung fields suggestive of healed Histoplasmosis

Koch's bacillus, fungi, *P. tularensis*, and routine pathogens with negative results. Antigen prepared from this pus and tested by Dr. F. G. MacMurray gave positive skin reactions in the patient and in a known cat scratch reactor, and no reaction in a known negative cat scratch reactor.

On November 30, 1954, the right axillary node was removed and the microscopic examination was reported by Dr. Grace Guin as chronic non-specific inflammation.

He was discharged on December 8, 1954, with no residual adenopathy and asymptomatic.

DISCUSSION

These cases are reported to emphasize that the diagnosis of cat scratch disease may be obscure. K. H. presents a typical picture of the disease, but G. R. presented such a multitude of significant findings that we were unsure of the diagnosis until six weeks after his discharge when the antigen prepared by Dr. MacMurray proved itself to be potent cat scratch testing material.

We believe that the pulmonary lesions of G. R. represent healed histoplasmosis, but we cannot explain the high titers against typhoid (H) and (O). These titers were repeated ten days later and found to be typhoid (H) 1:80, typhoid (O) 1:320. The boy was never immunized against typhoid and never had clinical typhoid fever. Multiple stool cultures were negative for *S. typhi*.

The etiology of cat scratch disease has not been proven, but there is probably a viral agent responsible. Daniels and MacMurray[1] in their study of 160 cases found 92 per cent with history of contact with cats although only 58 per cent had actually received a scratch. The usual time from the scratch to the development of the bubo was 7 to 21 days. Enlarged lymph nodes in the upper extremity appeared in 70 per cent of the cases and suppuration occurred in 29 per cent.

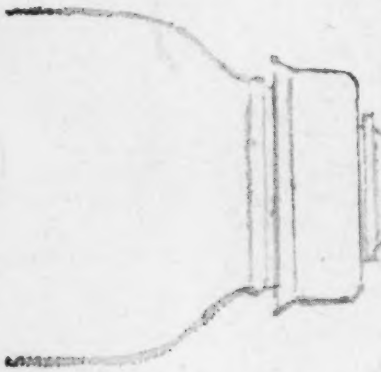
They recorded constitutional symptoms in 80 per cent of their patients, including chills, headache, aching, malaise, anorexia, and abdominal pain. Fever was common and lasted more than two weeks in 11 per cent of the cases. Two patients included in their series developed encephalitis following which there was complete recovery.

It is to be hoped that both the awareness of this disease and the availability of the skin-test antigen will increase. We are indebted to Dr. MacMurray for his cooperation in freely supplying his advice and the test antigens used on these children.

REFERENCE

1. Daniels, Worth B., and MacMurray, Frank G.: Cat Scratch Disease, Report of One Hundred and Sixty Cases, JAMA, **154**: 1247, 1954.

in infants allergic to cow's milk



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